Red Cell Disorders

Hemolytic anemias, Thalassemia, hemoglobinopathies

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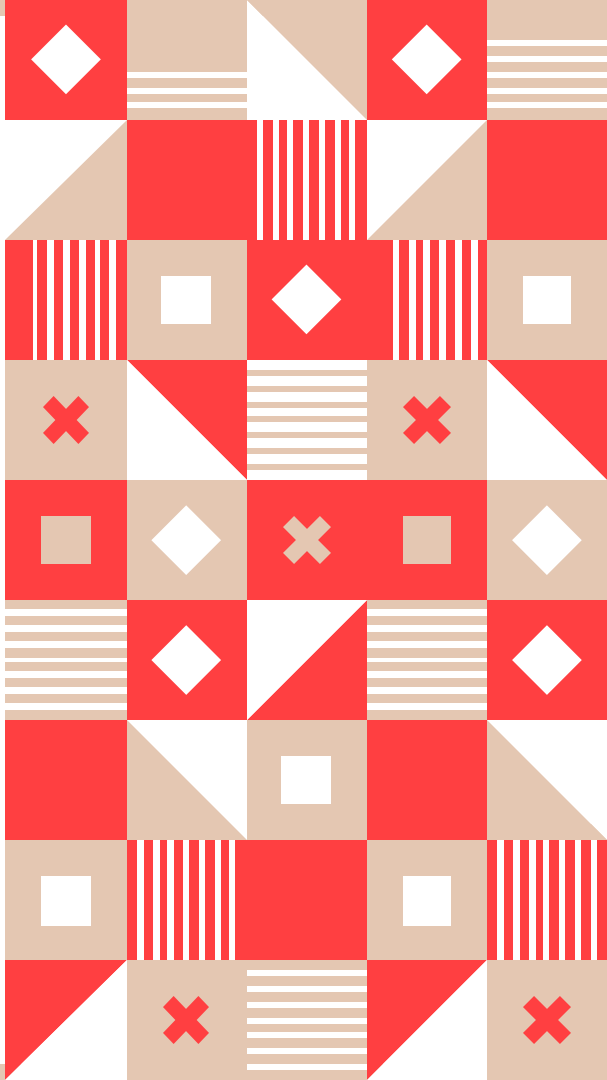
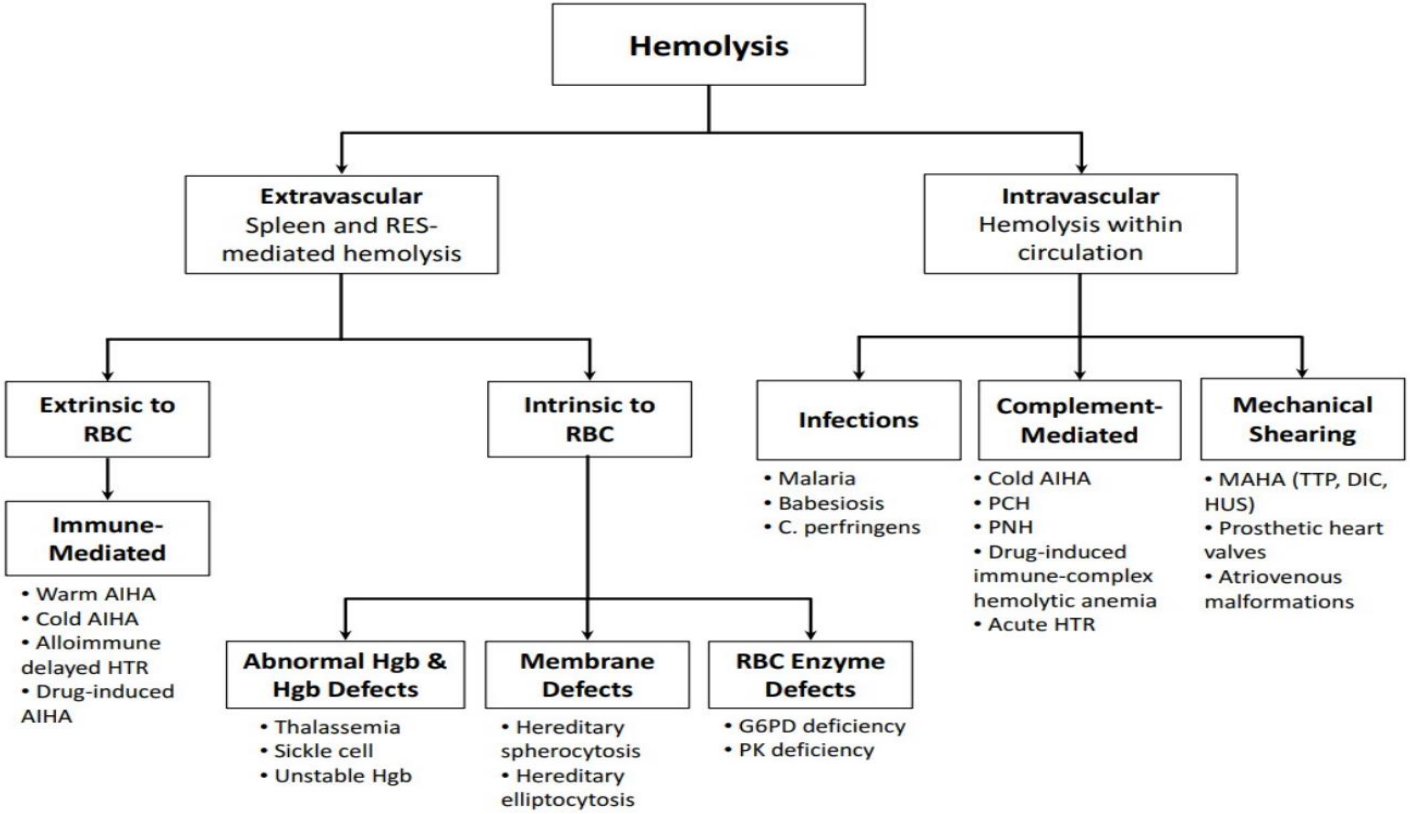
Hemolytic anemia

- A diverse group of disorders that have as a common feature accelerated red cell destruction (hemolysis).
- Two hallmarks: erythroid hyperplasia and reticulocytosis



Hemolytic anemia



hematologic

- both intravascular and extravascular hemolysis is decreased serum levels of *haptoglobin* .
- A plasma protein that binds free hemoglobin and is then removed from the circulation.
- Apparently macrophages “regurgitate” sufficient hemoglobin during consumption of red cells to cause haptoglobin levels to fall, even when hemolysis is entirely extravascular.

Extravascular hemolysis

- **Defects that increase RBCs destruction by phagocytes, particularly in the spleen.**
- The spleen contains large numbers of macrophages → responsible for the removal of damaged or antibody-coated RBCs from the circulation.
- RBCs go through extreme alterations of shape to navigate the splenic sinusoids.
- Any reduction in RBCs deformability makes this passage difficult, and they become “stuck”, recognized and phagocytosed by resident splenic macrophages.
- Clinical features:

- Hyperbilirubinemia and jaundice (degradation of hemoglobin in macrophages)
- Varying degrees of splenomegaly due to “work hyperplasia”
- If long-standing, formation of bilirubin-rich gallstones (pigment) and an increased risk of cholelithiasis

Intravascular hemolysis

- **Injuries so severe that red cells burst within the circulation**.
- may result from mechanical forces (e.g., turbulence created by a defective heart valve) or biochemical or physical agents that severely damage the red cell membrane (e.g., fixation of complement, or exposure to clostridial toxins or heat).
- Clinical features:

- *Hemoglobinemia, hemoglobinuria,* and *hemosiderinuria.*

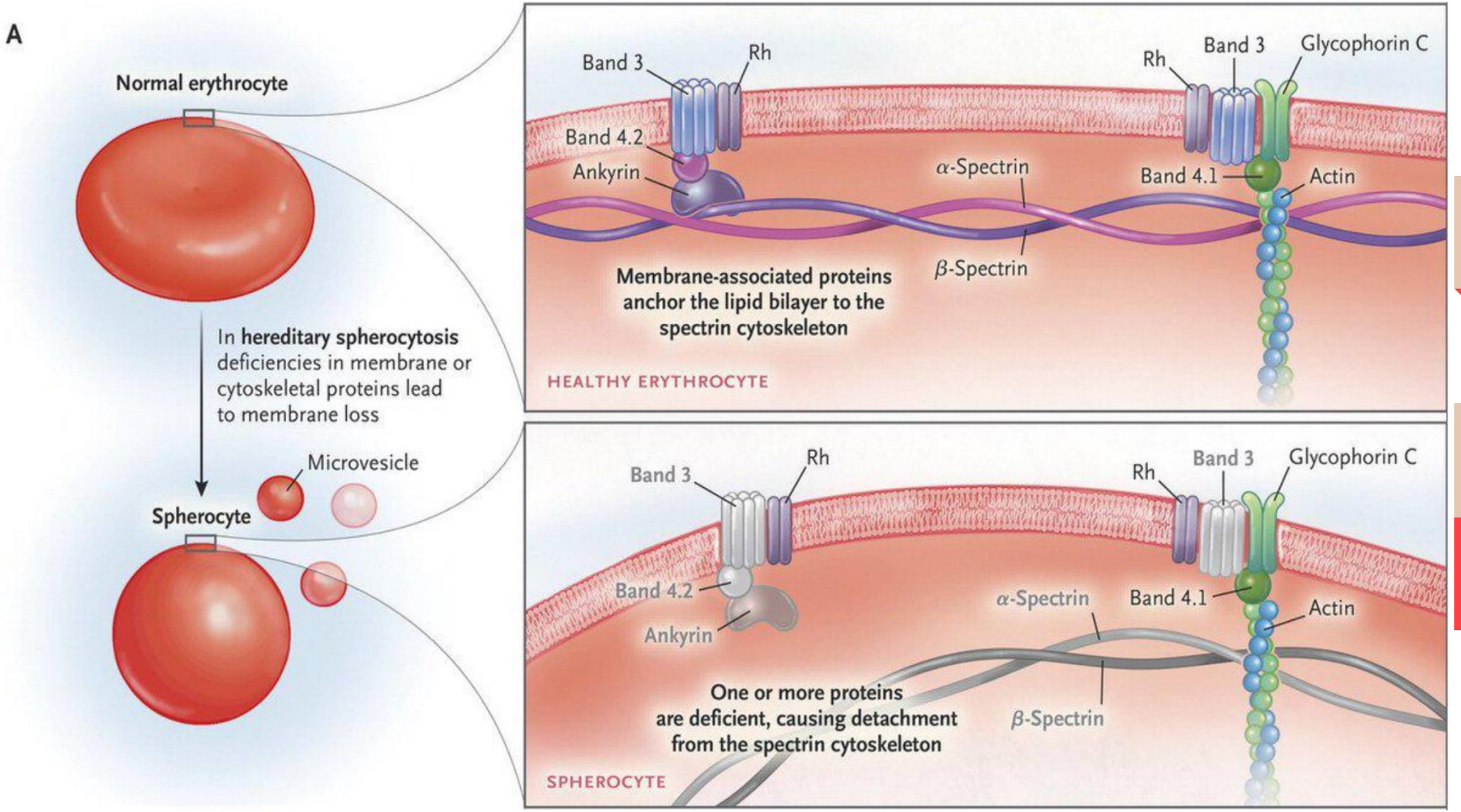
Hemoglobin released into the circulation is small enough to pass into the urinary space. Here, it is partially resorbed by renal tubular cells and processed into hemosiderin, which is then lost in the urine when renal tubular cells are sloughed.

- *Loss of iron,* may lead to iron deficiency if hemolysis is persistent.

By contrast, iron recycling by phagocytes is very efficient, and so IDA is not a feature of extravascular hemolytic anemias

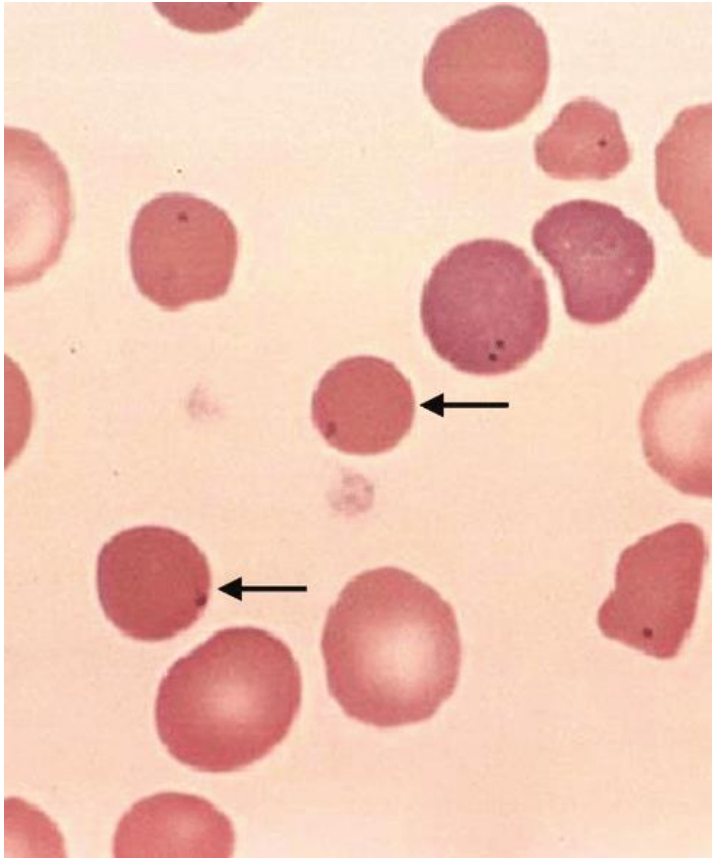
Hereditary Spherocytosis

- **An inherited (intrinsic) defects in the RBC membrane that lead to the formation of spherocytes nondeformable cells that are highly vulnerable to sequestration and destruction in the spleen**
- Usually **AD trait**. A more severe AR form affects a small minority.
- The defect is in the membrane skeleton, a network of proteins that stabilizes the lipid bilayer of RBC.
- Mutations most frequently involve ankyrin, band 3, or spectrin.
- These mutations weaken vertical interactions between the membrane skeleton & intrinsic red cell membrane proteins.
- This defect destabilizes the lipid bilayer → shed membrane vesicles into the circulation as they age.
- Little cytoplasm is lost in the process → surface area-to volume ratio decreases progressively with time → cells become **spherical**.


A
Normal erythrocyte
In hereditary spherocytosis deficiencies in membrane or cytoskeletal proteins lead to membrane loss
Microvesicle
Spherocyte
Band 3
Rh
Band 4.2
Ankyrin
α-Spectrin
β-Spectrin
Band 4.1
Actin
Glycophorin C
Membrane-associated proteins anchor the lipid bilayer to the spectrin cytoskeleton
HEALTHY ERYTHROCYTE
One or more proteins are deficient, causing detachment from the spectrin cytoskeleton
SPHEROCYTE

Clinical & morphology

- On smears, **spherocytes** are dark red & lack central pallor.
- Manifestations are anemia, splenomegaly, & jaundice
- Splenomegaly is more common and prominent in hereditary spherocytosis than in any other form of hemolytic anemia.
- Splenectomy improves the anemia → removing the major site of RBC destruction
- The course is stable, may be complicated by aplastic crises, the most severe of which are triggered by parvovirus B19 infection.

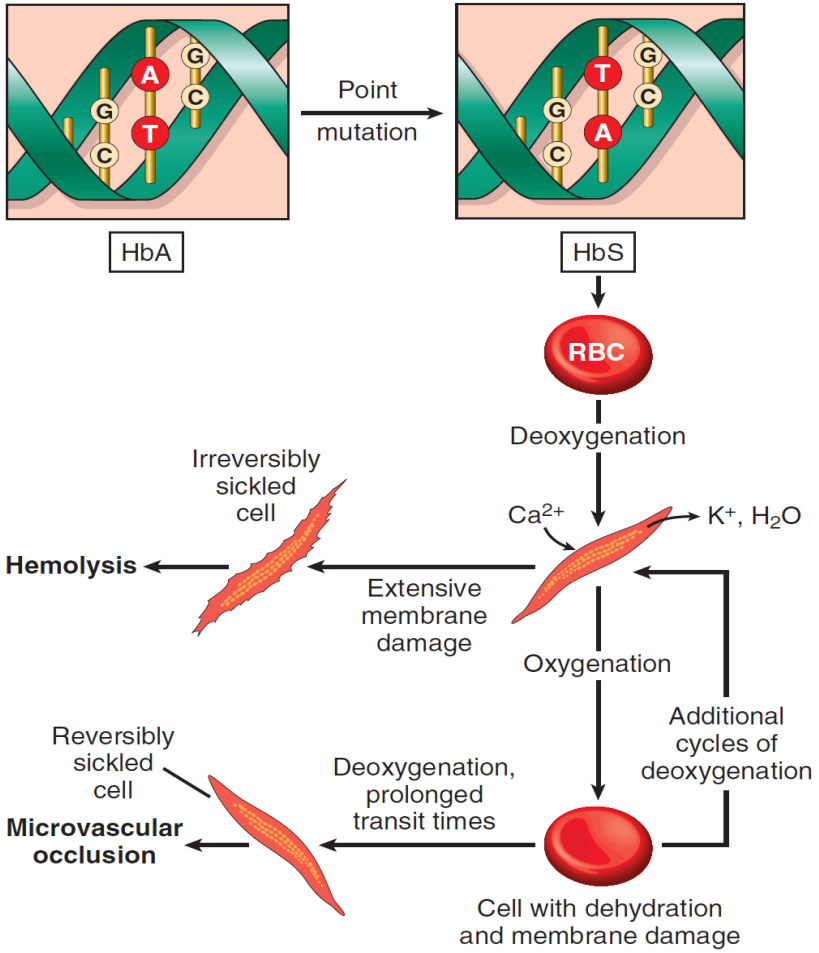


SICKLE CELL ANEMIA

- Hemoglobinopathies are a group of hereditary disorders caused by inherited mutations that lead to structural abnormalities in hemoglobin.
- Sickle cell anemia → the prototypic hemoglobinopathy.
- Caused by a mutation in β-globin → creates sickle hemoglobin (HbS).
- Sickle cell anemia is the most common familial hemolytic anemia.
- caused by a single amino acid substitution in β-globin (valine instead of a glutamate at the 6th amino acid position) → a tendency for deoxygenated HbS molecules to undergo a conformational change that allows polymers → distort the red cell → assumes an elongated crescentic (sickle shape).
- Sickle cell trait is the presence of one mutated and one normal β-globin gene: 40% of Hb is HbS and the remainder is HbA→ mostly asymptomatic.

The sickling of red cells..

- Risk factors: deoxygenation, dehydration, and acidosis
- Pathologic consequences:
  1. Chronic moderately severe hemolytic anemia → red cell membrane damage.
  2. Vascular obstructions, which result in ischemic tissue damage and pain crises.



SCA - Clinical Features

- Asymptomatic until 6 months of age →shift from HbF to HbS is complete.
- Anemia is moderate to severe; most patients have hematocrits of 18% to 30% (normal 38%–48%).
- Chronic hemolysis is associated with hyperbilirubinemia and compensatory reticulocytosis.
- Vasoocclusive crises: painful & lead to tissue damage and significant morbidity and mortality:

1. *Hand-foot syndrome*
2. *Acute chest syndrome*
3. *Stroke*
4. *Proliferative retinopathy*

SCA - Clinical Features

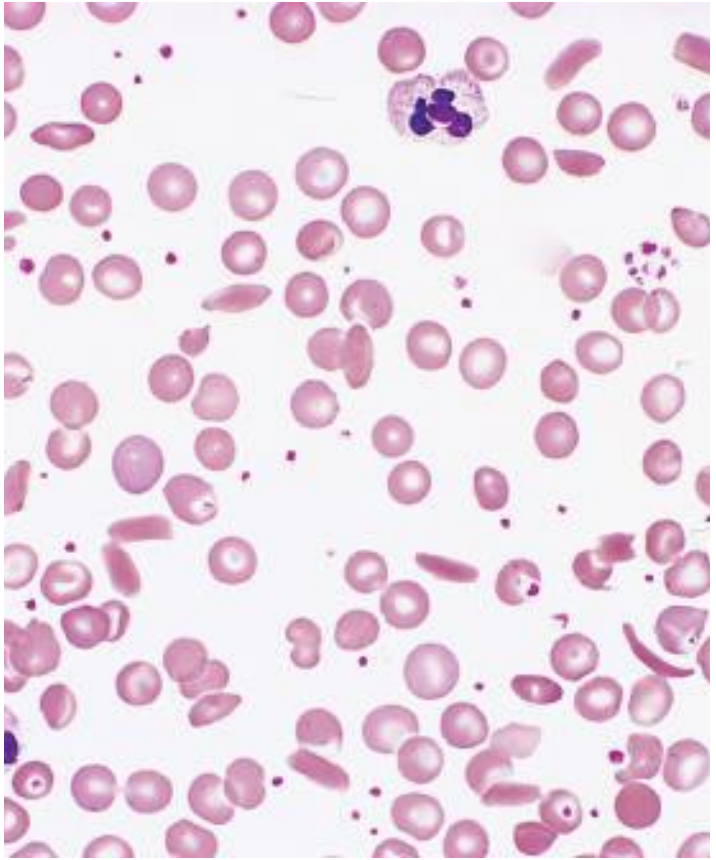
- **Splenomegaly:** moderate in children due to red pulp congestion → entrapment of sickled red cells.
- chronic splenic erythrostasis produces hypoxic damage & infarcts→ with time reduce the spleen to a useless of fibrous tissue → **autosplenectomy (**by adulthood)
- Being functionally asplenic → susceptible to infections caused by encapsulated bacteria (e.g; pneumococci)

- **Aplastic crisis***:* sudden decrease in red cell production→ erythroblasts infection with parvovirus B19*.*

- Severe, but self-limited

SICKLE CELL ANEMIA - Morphology

- PB: elongated, spindled, or boat-shaped **irreversibly sickled red cells.**

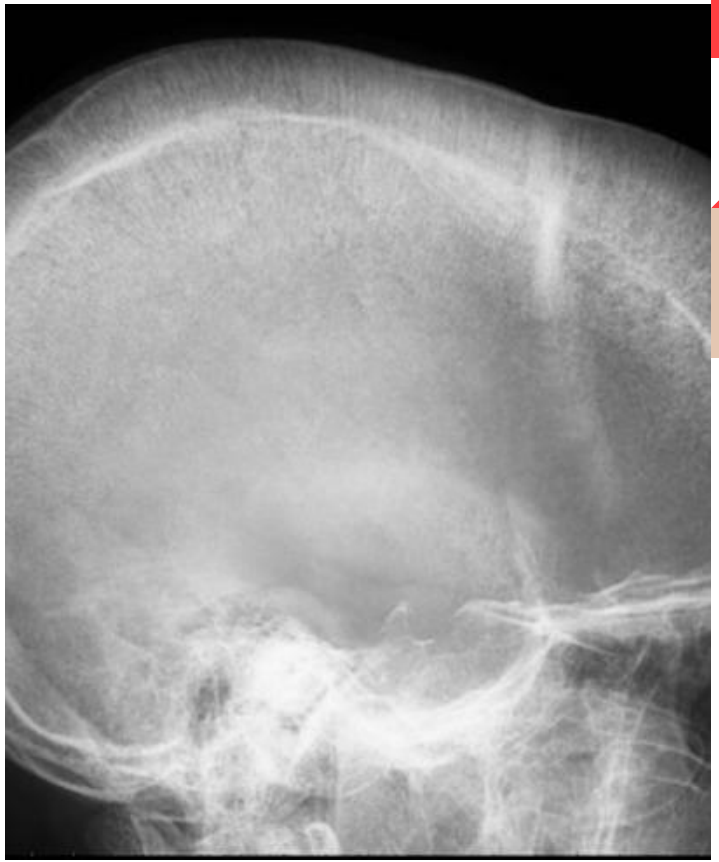


SICKLE CELL ANEMIA - Morphology

- A compensatory **hyperplasia of erythroid progenitors** in the marrow.

- Cellular proliferation in the marrow often causes bone resorption and secondary new bone formation, resulting in prominent cheekbones and changes in the skull resembling a “crewcut” in x-rays.

- Extramedullary hematopoiesis may appear in the liver and spleen.



Thalasemia

- **Inherited disorders caused by mutations in globin genes that decrease the synthesis of α- or β-globin → decrease hemoglobin→ microcytic anemia.**
- Thalassemia are particularly common in Mediterranean, African, and Asian regions
- Adult hemoglobin, HbA, is a tetramer composed of two α chains and two β chains. And thalassemia is divided into α- or β-thalassemia based on which chain have decreased production.

	Name	subunits
Adult	A	α2β2
Adult	A2	α2δ2
Fetal	F	α2γ2
Abnormal	H	β4
Abnormal	Bart's	γ4

β-Thalassemia

- Two β genes are present on chromosome 11.
- **Mutations** associated with β-thalassemia fall into two categories:

(1) β0, no β-globin chains are produced

(2) β+, reduced (but detectable) β-globin synthesis.

- Mutations are usually involving RNA splicing, β-globin gene promoter or coding regions.
- *β-thalassemia minor:* Persons inheriting one abnormal allele have *(β-thalassemia trait)*, which is asymptomatic or mildly symptomatic.
- *β-thalassemia major:* Most people inheriting any two β0 and β+ alleles

β-Thalassemias	
β-Thalassemia major	Homozygous β-thalassemia (β^0/β^0, β^+/β^+, β^0/β^+)
β-Thalassemia intermedia	Variable (β^0/β^+, β^+/β^+, β^0/β, β^+/β)
β-Thalassemia minor	Heterozygous β-thalassemia (β^0/β, β^+/β)

β-Thalassemia

- **Defective synthesis of β-globin in β-thalassemia contributes to anemia through two mechanisms:**

(1) inadequate HbA formation, resulting in small (microcytic), poorly hemoglobinized (hypochromic) red cells

(2) allowing the accumulation of unpaired α-globin chains → form toxic precipitates → severely damage RBC membranes and erythroid precursors apoptosis.

- leading to *ineffective erythropoiesis, iron overload and extravascular hemolysis.*

α -Thalassemia

- **caused mainly by deletions involving one or more of the α-globin**

Genes on chromosome 16

- The severity of the disease is proportional to the number of α-globin genes that are deleted

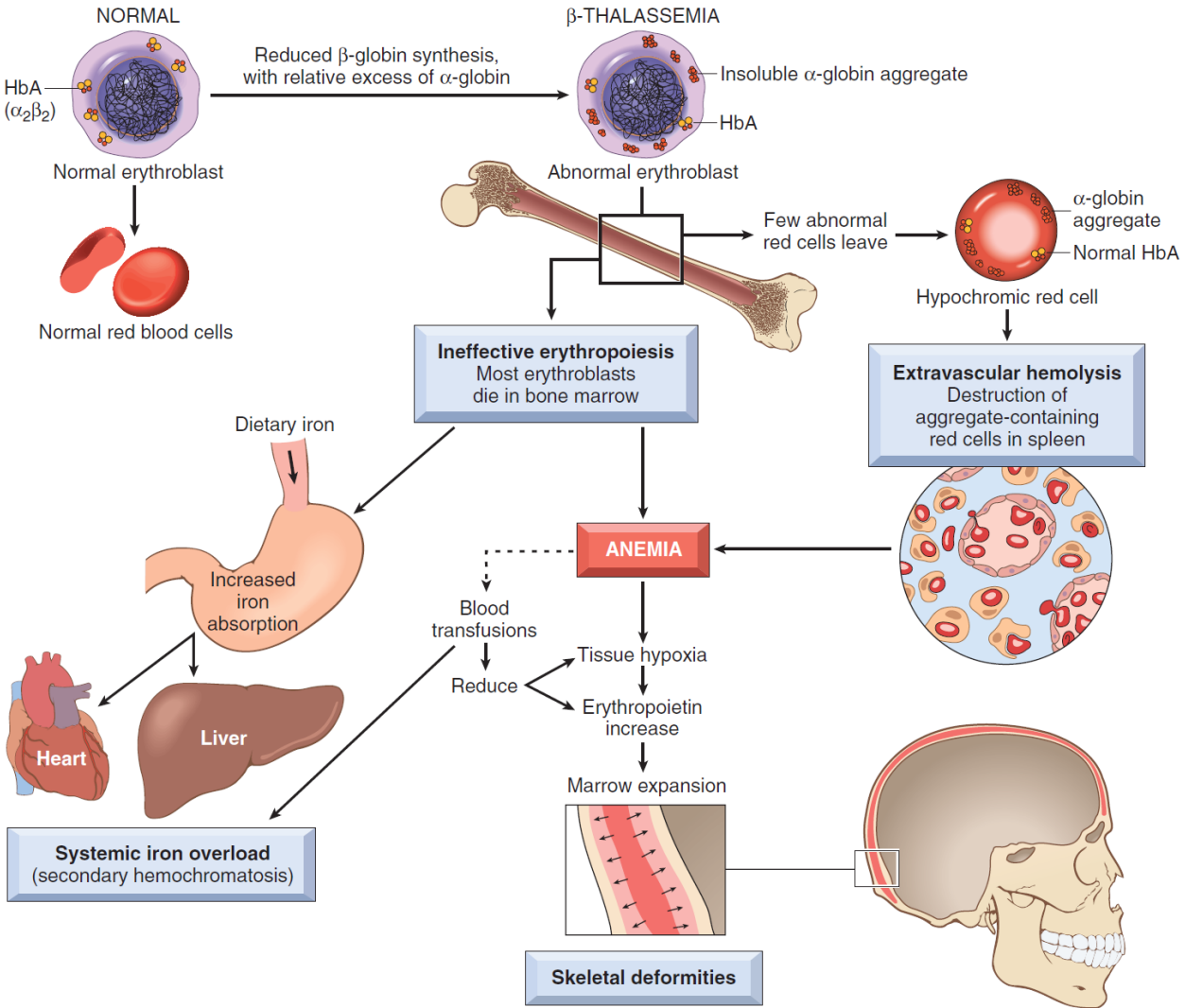
α-Thalassemias	
Silent carrier	–/α, α/α
α-Thalassemia trait	–/–, α/α (Asian)
	–/α, –/α (black African, Asian)
HbH disease	–/–, –/α
Hydrops fetalis	–/–, –/–

α -Thalassemia

- Excess β-globin and γ-globin chains form relatively stable β4 and γ4 tetramers known as *HbH* and *Hb Bart*, respectively, which cause less membrane damage than the free α-globin chains that are found in β-thalassemia → ineffective erythropoiesis is less common in α-thalassemia.
- Unfortunately, both HbH and Hb Bart have an abnormally high affinity for oxygen,which renders them ineffective at delivering oxygen to the tissues.

Clinical Features

- *β-Thalassemia trait* and *α-thalassemia trait* are typically asymptomatic, with mild microcytic hypochromic anemia; and generally, normal life expectancy.
- *β-Thalassemia major* manifests postnatally as HbF synthesis diminishes.
- Affected children → growth retardation.
- Patients are sustained by blood transfusions, which improve the anemia and reduce the skeletal deformities associated with excessive erythropoiesis. (survival to 2nd-3rd decade)
- Systemic iron overload gradually develops owing to inappropriate uptake of iron from the gut and the iron load in transfused red cells. (patients should be treated aggressively with iron chelators)


NORMAL
β-THALASSEMIA
HbA
($\alpha_2\beta_2$)
Reduced β-globin synthesis,
with relative excess of α-globin
Insoluble α-globin aggregate
HbA
Normal erythroblast
Abnormal erythroblast
Few abnormal
red cells leave
α-globin
aggregate
Normal HbA
Hypochromic red cell
Normal red blood cells
Ineffective erythropoiesis
Most erythroblasts
die in bone marrow
Extravascular hemolysis
Destruction of
aggregate-containing
red cells in spleen
Dietary iron
ANEMIA
Increased
iron
absorption
Blood
transfusions
Reduce
Tissue hypoxia
Erythropoietin
increase
Heart
Liver
Marrow expansion
Systemic iron overload
(secondary hemochromatosis)
Skeletal deformities

Thalassemia

- β-thalassemia minor and α-thalassemia trait: only peripheral blood abnormalities → microcytic hypochromic RBCs but regular in shape.
- β-thalassemia major: marked **microcytosis, hypochromia, poikilocytosis, anisocytosis.**
- Nucleated red cells (normoblasts) are also seen that reflect the underlying erythropoietic drive

- The expanded erythropoietic marrow may completely fill the intramedullary space of the skeleton, invade the bony cortex, impair bone growth, and produce **skeletal deformities.**

- Extramedullary hematopoiesis and hyperplasia of mononuclear phagocytes result in prominent **splenomegaly,** hepatomegaly, and lymphadenopathy

Thanks